REMARKS

This paper is responsive to the Office Action mailed April 21, 2003. Claims 35-60 are pending in this application and presently stand rejected. Reconsideration of the subject application in light of the amendments herein and the remarks that follow is respectfully requested.

The Pending Claims Meet the Requirements of 35 U.S.C. § 112, First Paragraph

The Examiner rejected claims 46-48, 56-58 and 59 under 35 U.S.C. § 112, first paragraph, as not being enabled by the specification. Regarding Claim 59, the Examiner asserts that *in vivo* gene therapy at the time of the invention was not sufficiently predictable and that the specification does not provide guidance as to how to practice the invention of Claim 59 without undue experimentation. The Examiner further cites four references, which ostensibly show that *in vivo* gene therapy is unpredictable and inefficient.

While these four references indicate that *in vivo* gene therapy, as a consistent treatment, still has problems to be solved, they all maintain that the process itself is possible. Deonarian (1998) states that, "viral methods for gene delivery have been studied for a number of years and are effective vectors for gene transfer." Verma (1997) points out that, "the use of viruses is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells." Crystal (1995) states that even "minimal correction of a genotype can have significant phenotypic consequences." Furthermore, "several studies have demonstrated that therapeutic genes transferred to humans by means of retrovirus, adenovirus, and plasmid-liposome vectors can evoke biologic responses that are relevant to the gene product and to the specific disease state of the recipient." Crystal, page 407. Finally, Romano (2000) reveals that, "a broad arsenal of gene transfer systems is currently available and is still in expansion." Therefore, it is evident that gene transfer protocols were known in the art at the time the present application was filed.

Claim 59 recites "a method of inducing insulin expression." The Examiner has not presented any evidence to suggest that inducing insulin secretion in a mammal does not have utility. Applicants have clearly shown (see 132 Declaration of Dr. Miller) that the invention results in an increase in insulin secretion *in vivo*. Increasing insulin secretion results in a lowering of blood glucose, which is a beneficial effect for mammals with higher than normal blood glucose levels. The Examiner appears to suggest that the unpredictably of

the art supports a claim that the pre-clinical data, which clearly shows effects on insulin secretion, will not occur in a clinical setting. Clinical data is not required to meet the enablement requirement of section 112. "Office personnel should not impose on applicants the unnecessary burden of providing evidence from human clinical trials. There is no decisional case law that requires an applicant to provide data from human clinical trials to establish utility for an invention related to treatment of human disorders." MPEP §2107.3. *See also In re Isaacs*, 347 F.2d 889. In fact, in the Examiner's obviousness rejection, the Examiner provides that an artisan of skill would have had "a reasonable expectation of success" using a GLP-1 expression vector in 293 cells (office action, p. 8). Thus, Applicants maintain that this claim is fully enabled.

The Examiner also argues that the present application fails to teach specific vectors, fails to provide working examples and fails to direct one skilled in the art to targeting strategies, which would allow one to practice the claimed invention without undue experimentation. Applicants respectfully traverse this rejection.

Undue experimentation would not be required for one of skill in the art to practice the present invention because the specification provides enough guidance when coupled with information that was in the art at the time the application was filed. Though some experimentation may be needed, the Court of Appeals for the Federal Circuit has determined that experimentation, though laborious, is not undue when the specification provides a reasonable amount of guidance. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988).

Applicants not only disclose specific vectors and targeting strategies, but also incorporate references (page 10, lines 15-29) that would allow a person of ordinary skill in the art to practice the present invention without undue experimentation. Furthermore, Applicants respectfully direct the Examiner's attention to the 37 CFR 1.132 Declaration of Dr. Miller, dated June 13, 2002. The data presented, generated following the teachings in the specification, demonstrate a working example showing that an immunologically masked stable cell line expressing GLP-1 (or an analog thereof) induces insulin expression.

The Examiner further questions whether the vectors of claims 46-48 and 56-58 are available to the public or, alternatively, whether instructions for their synthesis are adequately taught in the specification.

According to 37 C.F.R. 1.802 (b), "biological material need not be deposited unless access to such material is necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112." The specification provides precise instructions for

how to synthesize the vectors of claims 46-48 and 56-58 using materials available to the public and requiring no more than ordinary skill in the art; therefore, Applicants assert that deposit of the vectors of claims 46-48 and 56-58 is not required. The means of constructing the vectors of claims 46-48 and 56-58 are described in the specification in the following: Page 15, Example 2; page 18, Example 3; and page 20, Example 5. The starting material (*E. coli* K12 GM48) is deposited (see page 15, line 34 through page 16, line 3) and readily available, and the specification provides specific instructions for synthesizing the respective vectors. Therefore, Applicants respectfully request that this rejection be withdrawn.

The Pending Claims Meet the Requirements of 35 U.S.C. § 112, Second Paragraph

The Examiner rejected claims 35-60 under 35 U.S.C. § 112, second paragraph, for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 was rejected for using an improper Markush group. This error was corrected in the Claim Amendment section herein.

Claim 35 was rejected for use of the term "mammalian origin" which Examiner asserts is unclear and renders the claim indefinite. Absent "an express intent to impart a novel meaning to claim terms," terms in a claim take on their ordinary meaning. *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d at 1325. The customary and ordinary meaning of a claim term is assessed from the vantage point "of a person of ordinary skill in the field of the invention." *Dow Chemical Co. v. Sumitomo Chemical Co., Ltd.* 257 F3d at 1372. The term "mammalian origin" takes on its plain and ordinary meaning. Applicants maintain that this term is neither unclear nor indefinite.

Claim 35 was further rejected for use of the term "immunologically masked," which Examiner asserts is unclear and renders the claim indefinite. Applicants respectfully submit that this rejection is inappropriate and request reconsideration and withdrawal of the rejection. Methods useful for immunologically masking cells are known to one of skill in the art. The specification lists and provides citations (on page 10, line 35 through page 11, line 8) discussing various exemplary means of immunologically masking cells. Furthermore, the 37 CFR 1.132 Declaration of Dr. Miller, dated June 13, 2002, discusses on page 3 a method of immunologically masking transformed cells with purified F(ab')2 fragments. Therefore, Applicants respectfully request that this objection be withdrawn.

Claim 59 was rejected for use of the phrase "when incorporated into a cell." The Examiner asserts that the term is not clear. Applicants have amended claim to change the phrase to "integrated into the chromosomal DNA of the target cell." Support for this change can be found in the application on page 5, lines 30-34. This change renders the objection moot.

Finally, Claim 60 was rejected for use of the term "expressed in the introduced cells" which Examiner asserts renders the claim vague and indefinite. The Examiner sought clarity in the claim as to whether or not the expressed protein is secreted out of the cells and how insulin would act in regulating glucose levels. Applicants respectfully direct Examiner to the 37 CFR 1.132 Declaration filed by Dr. Miller dated June 13, 2002 wherein she described an animal study performed under her supervision, in which an immunologically masked, human cell line stably expressing Val8-GLP-1 was transplanted into diabetic rats and resulted in an increase in secreted Val8-GLP-1 and a resulting statistically significant increase in plasma insulin levels when compared to mock transplanted rats. Applicants respectfully request that this objection be withdrawn.

The Pending Claims Meet 35 U.S.C. § 103 Requirements

The Examiner is correct in presuming that the subject matter of all the claims was commonly owned at the time the invention was made.

The Examiner rejected claims 35-44, 49-55 and 60 under §103 as being unpatentable over Selden (US 6,048,724) in view of Pakzaban (Neuroscience 65:983-996, 1995). The Examiner states that Selden teaches human fibroblast cells that are transfected with an expression vector that encodes GLP-1 (17-37) and transplantation into a mouse. Pakzaban teaches that masking of donor MHC class I by F(ab')2 treatment resulted in enhanced survival of xenotransplants. The Examiner concludes that it would have been obvious to one of ordinary skill to treat the cells expressing GLP-1 with F(ab')2 before transplanting them in a mouse with a reasonable expectation of success. Applicants respectfully traverse this rejection.

The United States Supreme Court has stated that to make out a case for obviousness, one must: "(1) determine the scope and content of the prior art; (2) ascertain the differences between the prior art and the claims in issue; (3) determine the level of skill in the pertinent art; and (4) evaluate any evidence of secondary considerations." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). In addition, to support a *prima facie* case of obviousness

over a combination of prior art references, the Examiner must establish that the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The Federal Circuit has also stated that hindsight is not a justifiable basis on which to find an invention obvious. *See In re Dembiczak*, 175 F.3d 994 (Fed. Cir. 1999).

> Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field.

Id. at 999. Thus, to avoid hindsight analysis wherein the inventor's teachings are used against him/her, "there must be a rigorous application of the requirement for showing the teaching or motivation to combine the prior art references." *Id.* The Examiner's case must also include a finding that one of ordinary skill in the art at the time the invention was made, would have reasonably expected the claimed invention to work. *See In re O'Farrell*, 853 F.2d 894 (Fed. Cir. 1988). Further, it is inconsistent for the Examiner to argue that the references render the invention obvious while at the same time express doubt at the Applicants' ability to show the usefulness of the claimed invention. *Hybridtech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986).

In this case, none of the cited references explicitly or implicitly teach, suggest or motivate a skilled person to combine the references and arrive at the invention without using Applicants' specification. The Selden reference relates generally to a method of producing clonal cell strains that express erythropoietin or an insulintropin by transfecting the cell with exongenous DNA. The reference makes no suggestion whatsoever, of immunologically masking these cells. Pakzaban teaches only masking of donor MHC class I by F(ab')2 as used to prevent immunological rejection of neural xenotransplants. Again, there is no indicia of a suggestion or motivation to combine this technique with the Selden reference to arrive at the present invention. Furthermore, "the existence of each limitation of a claim in the prior art does not, by itself, demonstrate obviousness, because obviousness may not be established using hindsight. *Kahn v. General Motors Corp.*, 135 F.3d 1472, 1479 (Fed. Cir. 1998). Because there is no motivation to combine and the Examiner appears to be using impermissible hindsight to arrive at an obviousness rejection, Applicants respectfully request that this rejection be withdrawn.

The Examiner further rejected claim 45 as unpatentable over Selden and Pakzaban as applied to claims 35-44 and 49-55 above and further in view of Gromada (FEBS LETTERS 1995, 373:182-186). Gromada teaches only expression of the cloned human GLP-1 receptor in HEK 293 cells leads to the activation of more distal steps in the signal transduction pathway utilized by GLP-1. As mentioned above, there is no motivation to combine any of these references, and the addition of Gromada does not add anything that would render the present invention obvious. Applicants respectfully request that this rejection be withdrawn.

SUMMARY AND CONCLUSION

In view of the remarks and amendments enclosed and provided herein above, it is respectfully submitted that Examiner's rejections have been overcome. Applicants request reconsideration and withdrawal of the rejections. If Examiner feels that a telephone conversation with Applicants' attorney would be helpful in expediting prosecution of this case, the Examiner is invited to call Applicants' attorney.

Respectfully submitted,

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